ASAM REVIEW COURSE 2023

Sedative Use Disorder: Research and Practice

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Financial Disclosure

Ricardo Restrepo, MD, MPH

- No relevant disclosures

REVIEW COURSE 2023

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Outline

1. Historical View
2. Neurobiology
3. Epidemiology
4. Risk and Benefits of Benzodiazepines
5. Phases of Sedative-Hypnotic Treatment and related Syndromes
6. Selective nonbenzodiazepine hypnotic agents
7. Barbiturates
8. GHB
9. Conclusions

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Historical View

- First half of XX century Barbiturates (starting with Barbital)
- 1950 Meprobomate
- 1950s Benzodiazepine were introduced as substitute for barbiturates (starting with Chlordiazepoxide)
- 1960s Benzodiazepines widely available and prescribed
- 1970s Benzodiazepines became the most commonly prescribed of all medications around the world

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Historical View

- 1980s Identification of medication losing efficacy over time and became associated with adverse effects
- 1990s Short acting benzodiazepines
- 2000s (drug tolerance and withdrawal) Not sufficient for dependence and nonbenzodiazepine hypnotic agents; elderly population risks
- 2014-present DSM 5 (sedative use disorder); guidelines adopted regarding use

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Types of Sedatives

- BZ- receptor agonist (BZRA)
  - Benzodiazepines
  - Selective non-benzodiazepine hypnotics (Z-drugs)
- Barbiturates
- Others: GHB and Paraldehyde, chloral hydrate, meprobomate

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Case: RR

A year later, Mr. RR, now 59-year-old Latino male with a past history of ETOH use disorder, anxiety, insomnia, and past medical history of HTN, GERD, and pancreatitis, arrives in the emergency department with a friend for confusion and diaphoresis.

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Neurobiology (GABAA Receptor)

- GABA - the primary inhibitory neurotransmitter system in the CNS
- Transmembrane pentamer composed of:

2α , 2β

1γ

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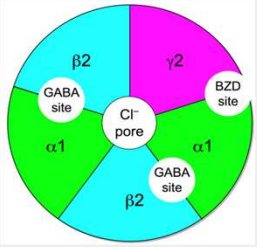
Neurobiology (GABAA Receptor)



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Neurobiology (GABAA Receptor)

- GABA is estimated to be present in 40% of all synapses in the human brain
- It is an inhibitory neurotransmitter, opposed to excitatory neurotransmitters such as glutamate.
- It reduces the excitability of the post synaptic side of the synapse
- 2 types : GABAA ionotropic (prominent target for drugs) and GABA B metabotropic
- BZDs increase the number of time the Cl- channel opens (frequency)
- BBTs increase the duration of the opening of the Cl-channel

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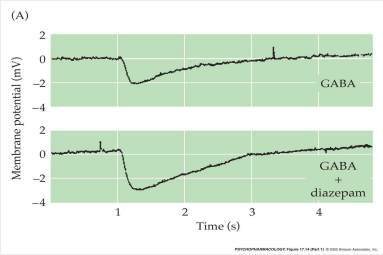
Effects of GABA and diazepam (benzodiazepine) on membrane potentials and chloride flux



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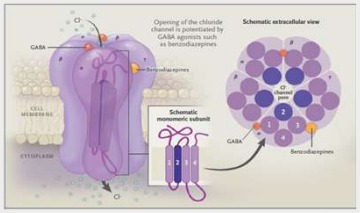
Neurobiology (GABAA Receptor)

Benzodiazepines require the presence of GABA

Barbiturates do not require the presence of GABA

Flumazenil blocks effects of benzodiazepine and zolpidem but not Barbiturates



Soyka, N Engl J Med 2017; 376:1147-1157

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Neurobiology (GABAA Receptor)

- Benzodiazepines
  - Bind a cleft of α and γ subunits
  - Increase the affinity of the receptor for GABA (frequency) : Chloride channel opening
  - BZD needs GABA
- Barbiturates (propofol):
  - Bind α subunit
  - Increase duration of channel opening
  - BBT does need GABA

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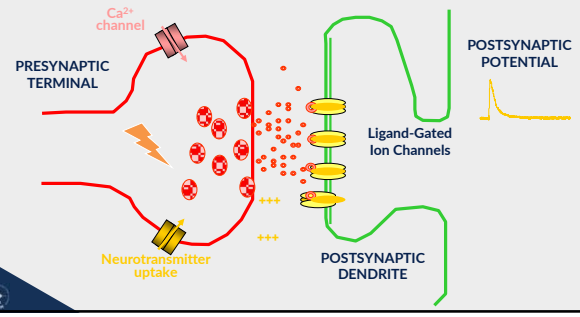
Steps in Synaptic Transmission



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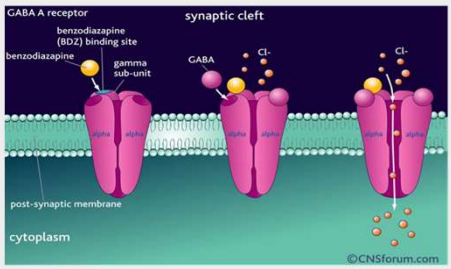
Neurobiology ($GABA_A$ Receptor)



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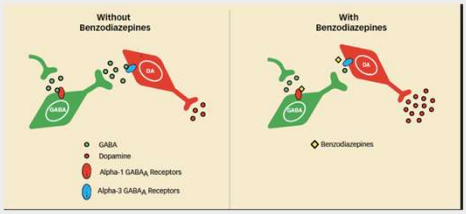
Mechanism of Benzodiazepine Addiction (hypothesis)



NIDA NOTES APRIL 19, 2012

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Epidemiology

- 80% of pts with benzo use disorder use other drugs
- 30-50% of pts with ETOH use disorders in detox and 44% of IV drug user also use BZD
- Average benzodiazepine use is about 2 :: 1

- Approximately 5.2 % of adults in U.S use benzos
- Use of benzodiazepines increases with age
- In the US, roughly 9 of 10 older adults who use benzodiazepines on a long-term basis are prescribed by PCP

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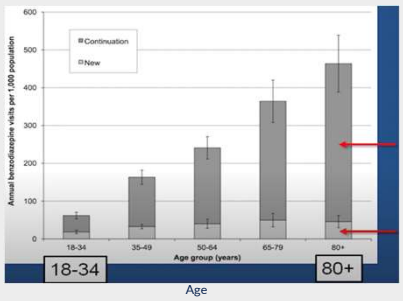
Epidemiology

Use of Benzodiazepine accumulates with age



Annual BZD visits per 1,000 population

Continuation

New

18-34

80+

Age

Maus et al. JAGS 2016

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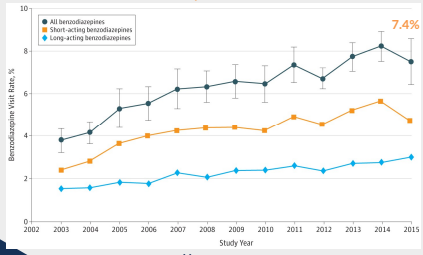
Epidemiology

Benzodiazepine Visit Rate in United States



7.4%

95% increase in BZD-related visits in 12 years

Benzo visit Rate %

Year

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4:2(1)

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Concurrent use of other Substances

- Rarely the initial or primary substance of abuse
- Rarely used alone to produced intoxication
- Usually abuse with other substances
- Healthy patients prefer placebo to benzodiazepines

- *ETOH use disorder patients and their offspring are more likely to experience mood elevation with benzodiazepines*

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Concurrent use of other Substances

- A high percentage of alcohol dependent patients use benzodiazepines regularly (29-76%)
- 70-96% of patients admitted to inpatient addiction treatment on high dose benzodiazepine use have concurrent dependence on other substances
- It is uncommon to see patients with substance use disorder just on benzodiazepines. Concurrent use with other drugs is common just with benzodiazepine use
- BNZD are prescribed in 1 out of 5 patients on opioids
- ⬆ Lethality when sedatives-hypnotics are combined with:
  - ETOH + BNZ
  - methadone + BNZ
  - buprenorphine + BNZ
  - Other CNS depressants + BNZ

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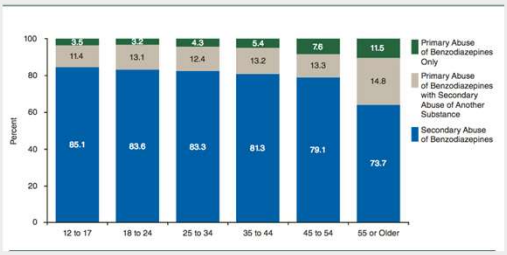
Epidemiology

Primary and Secondary Benzodiazepine Admissions, by Age in 2008



Note: Percentages may not sum to 100% due to rounding
Source: SAMHSA Treatment Episode Data Set (TEDS) 2008

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Benzodiazepines + Opioids

- Benzodiazepines (BZs) are the most frequently cited co-intoxicants involved in opioid-related morbidity and mortality.
- In 2010, the CDC reported 16,651 pharmaceutical opioid-related overdose deaths based on death certificate data- almost one of every three opioid-related deaths in 2010 also involved BZs
- On August 31, 2016, FDA issued a drug-safety communication about risks when opioid pain or cough meds are combined with BZs.

(Hwang et al., 2016; Jones, Mack & Paulozzi, 2013; DEA 2013)

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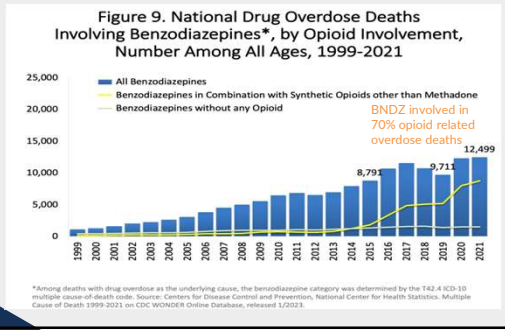
BZDs, by Opioid Involvement, Number among All Ages, 1999-2021



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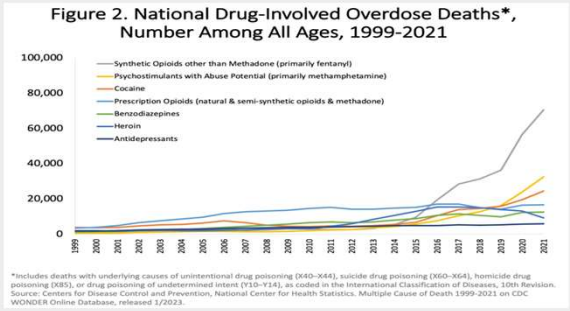
National Drug Overdose Involving Overdose Deaths, Number Among All ages, 1999-2021



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ED Visits: Risk of Serious Outcomes

	12-34 yo	35-44 yo	45-64 yo	65+
BZD alone	28%	30%	37%	39%
BZD + opioids	37%	43%	47%	59%
BZD + alcohol	35%	43%	51%	55%
BZD + opioids + alcohol	39%	47%	57%	70%

SAMHSA, DAWN Report, 12/18/2014

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Epidemiology

- Most frequent abused pharmaceutical second only to opioids
- Alprazolam is the most frequently abused followed by Clonazepam, Lorazepam, and Diazepam
- BZDs are prescribed at about 65.9 million office-based doctor visits. That's a rate of 27 annual visits per 100 adults

National Health Statistics Report that examined data from the 2014-2016 National Ambulatory Medical Care Survey (NAMCS) 2020.

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Prevalence of Benzodiazepine Use

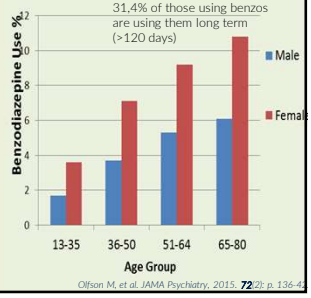
Benzodiazepines:

- Use is nearly twice as prevalent in women
- Increased utilization with increasing age
- Proportion of long-term use increases with age
- Prescribed at greater rates than antidepressants for the treatment of depression and anxiety

Bernardy NC, et al. J Gen Intern Med, 2013. 28(S2): p S542-8; Demyttenaere, K., et al.,. J Affect Disord, 2008. ***110****(1-2): p. 84-93.; Benitez, C.I., et al., Am J Geriatr Psychiatry, 2008.* ***16****(1): p. 5-13.; Maudsley Prescribing Guidelines in Psychiatry 12th Edition. 2015*

Figure 1. Prevalence of benzodiazepine use in the United States

In the oldest group (65-80)- 31,4% of those using benzos are using them long term (>120 days)



Olfson M, et al. JAMA Psychiatry, 2015. ***72****(2): p. 136-42*

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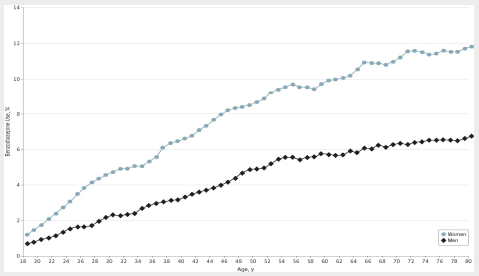
Epidemiology

BZD Use %



12% women

7% men

18 Age 80

Olfson M, et al. JAMA Psychiatry 2015;72(2):136-142.

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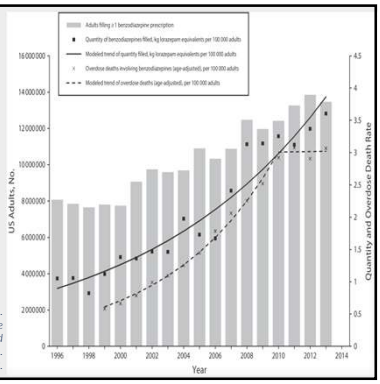
Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013

- Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67 percent, from 8.1 million to 13.5 million.



Olfson M. JAMA Psychiatry. 2015. 72(2): p. 136-42. Bachhuber MA et al Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. Am J Public Health. 2016;106(4):686–688.

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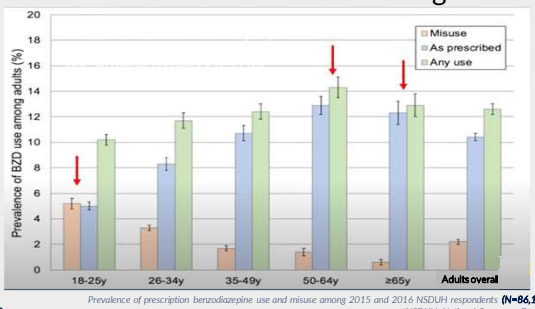
BZD use accumulates with age



Prevalence of prescription benzodiazepine use and misuse among 2015 and 2016 NSDUH respondents (N=86,186), by age group[a]
[a]NSDUH, National Survey on Drug Use and Health
Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. Psychiatr Serv. 2019;70(2):97-106. doi:10.1176/appi.ps.201800321

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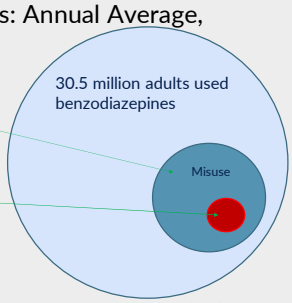
Benzodiazepine Use, Misuse, and Use Disorder Among Adults in the United States: Annual Average, 2015-2016

5.2 million adults misused benzodiazepines

0.5 million adults had benzodiazepine use disorders:

- 0.3 million had benzodiazepine dependence
- 0.2 million had benzodiazepine abuse



Blanco C, Han B, Jones CM, et al. Prevalence and correlates of benzodiazepine use, misuse, and use disorders among adults in the United States. J Clin. Psychiatry. 2018; 79(4)

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Case: RR

- Mr. RR did not receive his alprazolam refill from his PCP because, after taper, patient returned to his original dose and ran out of the prescription sooner. Mr. RR is upset and decided to see a psychiatrist who had planned to prescribe medication if ROI to contact PCP is signed.

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Case: RR

- Mr. RR reports that his heart has been racing and his insomnia has worsened; his friend states that, for the past four days, he has been having difficulty following conversations and focusing on daily tasks. He has been off alprazolam for seven days. Mr. RR denies any recent psychosocial stressors and does not endorse feelings of guilt, helplessness, or hopelessness. Furthermore, he denies any fever, nausea, vomiting, diarrhea, myalgia, abdominal cramps, or seizures. He denies any recent alcohol or illicit drug use.

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Factors associated with prescribing benzos

- Anxiety
- Insomnia
- Pain
- Chronic Medical Condition
- Female
- White
- Retirement Low income
- Elderly
- Smoking
- Poor Health
- >1 Prescriber
- Computer prescribing

Agarwal SD, Landon BE. JAMA Netw Open. 2019 Jan 4;2(1)

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Benzodiazepines and Addiction

Benzodiazepines are often not the primary substance abused and, when combined with other substances (e.g. alcohol, opioids), can have fatal consequences

- 5-10% - Patients newly started on benzodiazepines develop a substance use disorder
- 50% - Patients with substance use disorder history will develop a benzodiazepine use disorder
- 58-100% - Patients prescribed chronic benzodiazepines become physically dependent

Guina, J., et al., J Psychiatr Pract, 2015. 21(4): p. 281-303.; Substance Abuse: A Comprehensive Textbook (4th ed.). Baltimore, MD: Lippincott. Williams & Wilkins. 2004. pp. 302-312.; Substance Abuse and Mental Health Services Administration. The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines. . Rockville, MD., June 2, 2011.

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Benefits and Risks

- Population
  - Therapeutic dose dependent
  - Prescribed high-dose dependent (sedative use disorder)
  - Recreational benzodiazepine use
- Risk factors for benzo use disorder:
  - Longer duration of BNZ use
  - Higher Benzodiazepine doses
  - Lower level of education
  - Greater insomnia severity
  - Current antidepressant use

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Benefits and Risks

ACTION		CLINICAL USE
Anxiolytic	Relief of anxiety	Anxiety and panic disorders, phobias
		Agitated Psychosis
Hypnotic	Promotion of sleep	Insomnia
Myorelaxant	Muscle relaxation	Muscle spasms, spastic disorders
Anticonvulsant	Stop fits, convulsions	Fits to drug poisoning, some form of epilepsy, alcohol withdrawal
Amnesia	Impairment of short-term memory	Premedication for operations, sedation for minor surgical operations

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Benefits and Risks
–prior prescribing benzodiazepines-

TOLERANCE and DOSE ESCALATION = WITHDRAWAL

- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic
- Short term use (4 weeks)

Royal College of Psychiatrists and The British Association for Psychopharmacology 2013

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Benefits and Risks (concerns)

- Long term use have shown deficits in: learning, memory, attention and visual spatial ability
- Anterograde Amnesia
- Adverse effects:
  - May contribute to psychomotor impairment and increase the risk of falls and automobile accidents
  - Psychomotor impairment is characterized by:
    - Slow reaction time
    - Diminish speed and accuracy for motor tasks
- Increase risk of hip fractures (50% increase risk) and recurrent falls in the elderly population
- OD with Benzodiazepine alone are almost never lethal (high therapeutic index) but OD with BBT alone can be
- Withdrawal symptoms prolong sedative overuse

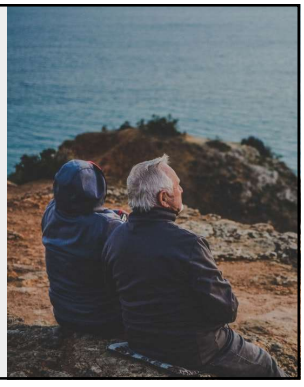
Falls | Hip Fractures | Sedation | Cognitive impairment

Cumming et al. Benzodiazepines and Risk of Hip Fractures in Older People. CNS Drugs17,2003

41

Benefits and Risks (concerns)

- The 2015 American Geriatrics Society Beers Criteria recommend avoiding benzodiazepines in this population. Despite these consensus recommendations and known risk factors:
  - Benzodiazepine use is three times more prevalent in older adults compared to younger adults
  - Roughly one-quarter of long-term benzodiazepine use is in patients ≥65 years of age



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Considerations when prescribing BZs

- Examine the risk-benefit ratio
- Avoid nonbenzodiazepine hypnotic (Alternative)
- Inform patient of planned duration of therapy
- Prescribe for brief periods
- No refills without follow up
- Use random urine toxicology
- Attempt to taper dose
- Always check the Prescription Drug Monitoring Program (PDMP) before and during the treatment
- Formalize written treatment agreement

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Phases of Sedative-Hypnotic Treatment and Related Syndromes

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Equivalent Doses and Elimination half-lives of benzodiazepines

BENZODIAZEPINES	APPROXIMATELY EQUIVALENT DOSAGE (mg)	ELIMINATION HALF-LIFE (hrs)- (active metabolite)
Alprazolam *	0.5	6-12
Chlordiazepoxide	25	5-30 (36-200)
Clonazepam*	0.5	18-50
Diazepam	10	20-100 (36-200)
Flunitrazepam	1	18-26 (36-200)
Flurazepam	15-30	(40-250)
Lorazepam*	1	10-20
Oxazepam	20	4-15
Temazepam	20	8-22
Triazolam*	0.5	2

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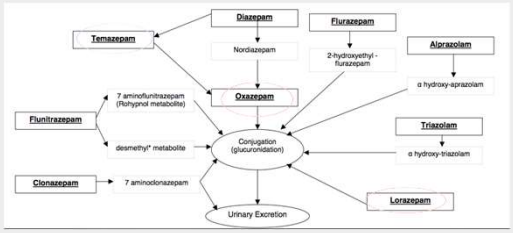
Benzodiazepine Metabolism



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Types of Benzodiazepines

- 2-Keto benzodiazepines (Clonazepam, Diazepam, Chlordiazepoxide)
  - All have long half-lives (23-100 hours)
  - All have active metabolites (commonly desmethyldiazepam)
  - Some administered as Prodrug
- 3-Hydroxy Benzodiazepines (Oxazepam, Temazepam, Lorazepam)
  - Intermediate half-lives (most 10-15 hours)
  - No active metabolites (better in elderly/hepatic impaired)
  - Metabolized outside the liver (only need glucoronidation)
- Triazolo Benzodiazepines (Alprazolam, Triazolam)
  - Short to Intermediate half lives (anywhere from <12 hours)
  - Some have active metabolites

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Pharmacokinetics

BZDs are differentiated by their pharmacokinetic profiles, based on lipophilicity and metabolism:

- **Half-life** (short, intermediate, long)
- **Onset-of-action** (rapid, intermediate, slow)
- **Metabolic pathways** (with or without active metabolites, with or without P450 involvement)
- Pharmacokinetics are affected by:
  - Routes of administration
  - Rates of absorption
  - Rates of elimination

Clinical Pharmacology 2017

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Pharmacokinetics

LONG ACTING	MEDIUM ACTING	SHORT ACTING
• Chlordiazepoxide	• Lorazepam	• Alprazolam
• Diazepam	• Oxazepam	• Triazolam
• Clonazepam	• Temazepam	• Midazolam

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Case: RR

PE: He was found to be tachycardic (pulse, 110 beats/min) and hypertensive (blood pressure, 170/90 mm Hg). His medical workup, including CBC count, electrolyte panel, liver function tests, blood glucose level, and urine toxicology screen were within normal limits.

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Case: RR

MSE: Casually dressed male who appeared to be restless and irritable with twitches in his face and complains about tinnitus. He was oriented to time, place, and person. His speech was normal in rate and content. His mood was subjectively anxious and objectively dysphoric, and his affect was congruent with mood. His thought form was linear and goal directed. There was no evidence of paranoid ideations/delusions. He denied any auditory or visual hallucinations. He scored 30/30 on the Mini-Mental State Examination. He had good insight and judgment. He endorsed passive suicidal ideations, no plan. He denied any homicidal ideations

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Management of Benzodiazepine Withdrawal

Variable presentation:

- There are no pathognomonic signs and symptoms of benzodiazepine withdrawal
- Assess for subjective and objective symptoms
- May have few concurrently observable hyper-adrenergic signs or vital sign fluctuations (unlike acute alcohol withdrawal)

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Symptoms of anxiety state	Symptoms less common in anxiety states-relatively specific to benzodiazepine withdrawal
Anxiety, panic attacks, agoraphobia	Perceptual distortions, sense of movement
Insomnia, nightmares	Depersonalization, derealization
Depression, dysphoria	Hallucinations (visual, auditory)
Excitability, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light headedness	Formication (skin "crawling")
Weakness "jelly legs"	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness	Tinnitus
Sweating, night sweats	Psychotic Symptoms
Palpitations	Confusion, delirium
Blurred or double vision	Convulsions

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Management of Benzodiazepine Taper

Challenging process for both patients and doctors if you do not have a treatment plan

Strategies:

- Gradual dosage tapering (avoid prn dosing)
- Psychological Support
- Reasons for prescribing
- Lifestyle
- Personality

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Management of Benzodiazepine Taper

- Take into account dosage and type of benzodiazepine
- Environment stresses
- Amount of available support
- Prepare for months or a year for the taper
- Individualize treatment adjusted to patient's needs (personalized treatment)

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Management of Benzodiazepine Withdrawal /Taper

Time course and severity are influenced by:

- Duration of use: short vs. long term use
- Dose: low/therapeutic dose vs. high dose
- Pharmacokinetics: short vs. long acting
- Host factors: comorbid pathology or substance use disorder

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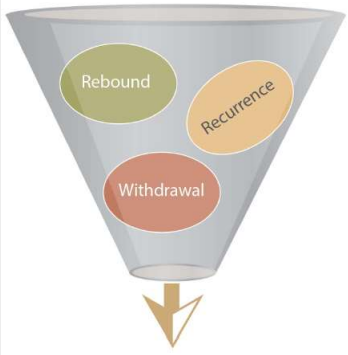
What is the difference between withdrawal, rebound and recurrence?

- Recurrence: the person experiences the same symptoms and severity of symptoms that existed prior to treatment
- Rebound: occurs when a drug is withdrawn and the individual experiences anxiety symptoms that are more severe than those experience prior treatment
- Withdrawal: the time-limited development of unique symptoms as the result of discontinuing or decreasing the use of a psychoactive drug



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Management of Benzodiazepine Withdrawal

Time and Severity can vary

- Short Acting BZs and those with active metabolites when stopped, can lead to WD sx within hours
- Long Acting BZs with active metabolites can take 48 hours – 7 days for WD sx to emerge
- Severe WD from BZs can be accompanied by delirium

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Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

- >10 days use with therapeutic dose: some experience transient insomnia
- <2 weeks with therapeutic dose: Most experience rebound
- >2 months with therapeutic dose: Most experience mild withdrawal

Of patients who take a benzodiazepine for more than a month, 47% (n=1048) become dependent

De Las Cuevas et al 2003

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Management of Benzodiazepine Withdrawal

Duration of use and therapeutic dose:

- >4 to 6 months with therapeutic dose;
- Most experience mild to moderate withdrawal
- >12 months with therapeutic dose:
- 20-80% experience moderate to severe withdrawal

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Management of Benzodiazepine Withdrawal: When to Taper

- Over-sedation
- Cognitive impairment
- Concurrent Rxs or use of high-risk CNS depressants medications
  - Other BZs, non-BZ hypnotics, and OPIOIDS
- Alcohol use disorder and other SUDs
- Overuse, misuse, or BZ use disorder
- Patient request
- Other

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MANAGEMENT/Systematic discontinuation

- Tapering
- Substitution and tapering

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MANAGEMENT/Systematic discontinuation

- Rate for dosage varies for different types of benzodiazepine pts:
- Withdrawal shows in 1- 7 days depending on half lives
- One-eight to one-tenth of the daily dose (10-25% weekly)
- Taper between 4 weeks to 6 months or even more

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Management of Benzodiazepine Withdrawal

Pharmacological /Strategies Treatment of Withdrawal

- Taper over months:
- Convert to longer acting agent like Clonazepam, Chlordiazepoxide, Diazepam)
- Taper gradually while starting alternative therapies if needed (months)
- Rebound psych meds for anxiety/sleep (Trazadone, Mirtazapine, Buspirone)
- Use of Anticonvulsant carbamazepine or valproate

Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005; 18:249-255.

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When do you see withdrawal symptoms?

- Short-acting BZD: oxazepam, triazolam, temazepam, alprazolam
- Short acting sedative-hypnotics: pentobarbital, secobarbital, meprobamate, metaqualone
  - Withdrawal onset in 12-24 hrs with
  - Peak of withdrawal intensity-day 1 to 5
  - Duration of acute withdrawal- 7 to 21 day

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When do you see withdrawal symptoms?

- Long-acting BZD and sedative-hypnotics: diazepam, chlordiazepoxide, phenobarbital
  - Withdrawal Onset within 5 - 14 days of cessation
  - Peak of Withdrawal Intensity - Days 1 to 9
  - Duration of Acute Withdrawal - 10-28 days
    - Protracted withdrawal symptoms for months

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Phenobarbital Substitution and Taper

- Substitution of benzodiazepine with equipotent dose of phenobarbital
- For inpatient, medically monitored setting only
- Effective Strategy for:
  - High dose dependent
  - Poly-Substance Dependence
  - Concurrent Alcohol/other Sedative Hypnotic
  - Unknown or erratic polypharmacy drug use

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Phenobarbital Substitution and Taper

- Establish Stabilization Dose by Computing Phenobarbital equivalents
  - Alprazolam 1 mg=PB 30 mg
  - Clonazepam 2mg=PB 30 mg
  - Diazepam 10 mg=PB 30 mg
  - Lorazepam 2 mg=PB 30 mg
  - Carisoprodol 700 mg=PB 30 mg
- PB should be give TID or QID
- Maximum PB starting dose 500mg/day

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Phenobarbital Substitution and Taper

- Monitor patient for signs of toxicity before administering each dose
- Signs of PB toxicity are easy to observe:
  - Sustained horizontal nystagmus
  - Ataxia
  - Slurred Speech
- If intoxication observed:
  - If 1 sign of toxicity observed, skip one dose
  - If 2 signs of toxicity observed, skip 2 doses
  - Recalculate new daily dose

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Phenobarbital Substitution and Taper

- Once stabilization dose is established: maintain patient on initial dose for two days
- If patient has neither signs of withdrawal or toxicity, then patient is moved to the withdrawal phase
- Decrease phenobarbital 30 mg/day unless signs of toxicity or withdrawal are seen
- If patient develops objective signs of withdrawal. Daily dose is adjusted upward by 50% and patient is stabilized before continuing withdrawal

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Pregnancy

- Pregnant and lactating women are relatively contraindicated due to:
  - Ability of benzodiazepines to cross fetal placental barrier and to pass into breast milk
  - Teratogenic effects
  - Floppy baby syndrome
  - Neonatal withdrawal

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Flumazenil

- Reverse the sedation produced by a benzodiazepine (Acute O.D with benzodiazepine)
- Nonspecific competitive antagonist of benzodiazepine receptor
- May up regulate BZ receptors
- IV use 1 mg monitor pt every 30-60 minutes
- Adverse effects: seizures, cardiac arrhythmias and acute precipitated withdrawal

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Z-Drugs (Selective nonbenzodiazepine hypnotics)

- Zaleplon
- Zolpidem
- Eszoplicone
- Zoplicone*

- Lower the risk for residual daytime drowsiness due to shorter duration of action
- Short term use
- Bind to sub-types of GABAAreceptors – α1 subunit that specifically modulate sleep and therefore are thought to have less unwanted side effects

- SE: risk of increased sleep- related behaviors

- Apply the general principles prescribing benzodiazepines to the Z-drugs

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Barbiturates

- The oldest sedative hypnotics
- Classified in three different pharmacokinetics category
- In the past used for treatment of anxiety disorders
- BBT: low therapeutic index
- Replaced by benzodiazepines
- BBT induce the synthesis of hepatic cytochrome P450, thus alter their own metabolism and the metabolism of other meds

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Barbiturates

Duration of Action	LS	Onset	Duration	Use
Ultrashort	H	10-20 s	20-30 min	IV anesthesia
Thiopental				
Methohexital				
Short/Intermediate	M	20-40 min	5-8 h	Surgical anesthesia and sleep induction
Amobarbital				
Secobarbital				
Pentobarbital				
Long	L	Over 1 h	10-12 h	Prolong sedation and seizure control
Phenorbarbital				
Meprobarbital				

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GHB
Gamma-Hydroxy-Butyrate

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"When I wake up,
I feel completely refreshed.
In comparison to the other drugs that
are supposed to be 'clean,'
G really is clean."

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FDA approved: Narcolepsy with cataplexy

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Effects

- Sensual drug, like MDMA, but also resulting in "the greatest sex ever."
- Relaxation, tranquility, placidity, mild euphoria, disinhibition.
- Temporary amnesia (hence "the date rape drug").
- Has been used as a muscle developer and fat burner

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Neurobiology

- GHB is a neurotransmitter.
- Short half life (30 minutes)
- It is both a precursor and a metabolite of GABA.
- Activity on both the GABAB and the GHB binding sites, results in:
  - Temporary suppression of dopamine,
  - Subsequent marked release of dopamine, and
  - Increased release of endogenous opioids.
- Also it is a highly regulated Schedule III medication for narcolepsy (Xyrem).

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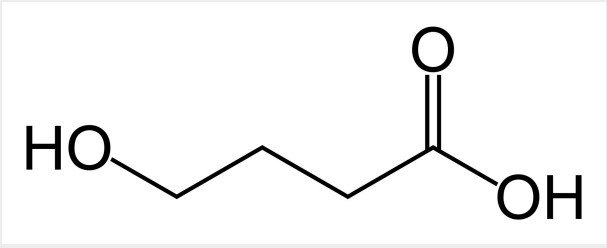
The Molecular Structure



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Intoxication

- Steep dose-response curve:
  - Ataxia, loss of coordination.
  - Respiratory depression, bradycardia, hypotension
  - Coma, persistent vegetative states, death
  - Overdose is a real danger (LD50 is only 5 times the recreational dose).
  - Synergistic effect with alcohol/other sedatives.
- Treat as a medical emergency:
  - ABCs, consider Intensive Care Unit admission.
  - Atropine for bradycardia.

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Withdrawal

- Withdrawal is rare but severe.
- Mild withdrawal may persist for several weeks after cessation of use:
  - Anxiety, tremor, insomnia.
  - "Feelings of doom."
- Severe withdrawal resembles barbiturate withdrawal:
  - Treat with benzodiazepines.

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Long Term Features

- Physiological dependence.
- Most patients who overdose on GHB recover completely.
- No FDA approved medications.
- MET and CBT are the major treatment modalities.

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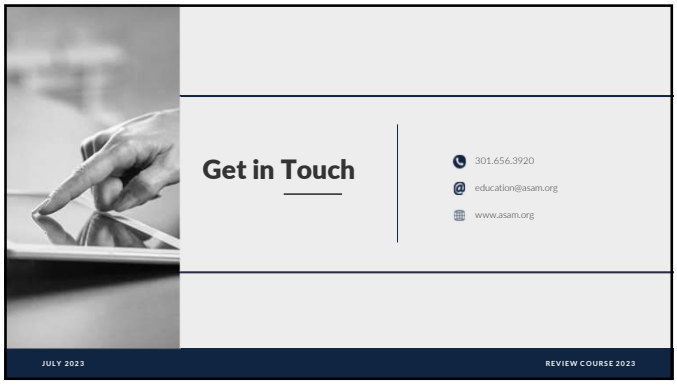
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